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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No.	6488.US.02
First Inventor or Application Identifier	Steven L. Krill et al.
Title	SOLID DISPERSION PHARMACEUTICAL FORMULATIONS
Express Mail Label No.	EL 384 167 796 US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

1. [X] * Fee Transmittal Form (e.g., PTO/SB/17) (Submit an original and a duplicate for fee processing)
2. [X] Specification [Total Pages 29] (preferred arrangement set forth below)
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings (if filed)
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [X] Drawing(s) (35 U.S.C. 113) [Total Sheets 5]
4. Oath or Declaration [Total Pages]
   a. [ ] Newly executed (original or copy)
   b. [ ] Copy from a prior application (37 C.F.R. § 1.63(d)) (for continuation/divisional with Box 16 completed)
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

5. [ ] Microfiche Computer Program (Appendix)
6. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
   a. [ ] Computer Readable Copy
   b. [ ] Paper Copy (identical to computer copy)
   c. [ ] Statement verifying identity of above copies

JC813 U.S. PTO 09/709824 11/10/00

ACCOMPANYING APPLICATION PARTS

7. [ ] Assignment Papers (cover sheet & document(s))
8. [ ] 37 C.F.R.§3.73(b) Statement (when there is an assignee) [ ] Power of Attorney
9. [ ] English Translation Document (if applicable)
10. [X] Information Disclosure Statement (IDS)/PTO-1449 [8] Copies of IDS Citations
11. [ ] Preliminary Amendment
12. [X] Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
13. [ ] * Small Entity Statement(s) (PTO/SB/09-12) [ ] Statement filed in prior application Status still proper and desired
14. [ ] Certified Copy of Priority Document(s) (if foreign priority is claimed)
15. [X] Other: See 1 in Addendum

*NOTE FOR ITEMS 1 & 13 IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

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Prior application information: Examiner _____ Group / Art Unit: _____
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Name (Print/Type)	Steven R. Crowley	Registration No (Attorney/Agent)	31,604
Signature		Date	11/10/2000

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TOTAL AMOUNT OF PAYMENT ($) 728.00

Complete if Known	
Application Number	
Filing Date	November 10, 2000
First Named Inventor	Steven L. Krill et al.
Examiner Name	
Group / Art Unit	
Attorney Docket No.	6488.US.02

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

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[X] Charge Any Additional Fee Required Under 37 CFR 1.16 and 1.17

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	($)	Small Entity Fee Code	($)	Fee Description	Fee Paid
101	760	201	380	Utility filing fee	710.00
106	310	206	155	Design filing fee	
107	480	207	240	Plant filing fee	
108	760	208	380	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($) 710.00

2. EXTRA CLAIM FEES

	Extra Claims		Fee from below		Fee Paid
Total Claims	21 -20**=	1	X 18.00	=	18.00
Independent Claims	1 -3**=	0	X 80.00	=	0.00
Multiple Dependent			270.00	=	0.00

***or number previously paid, if greater; For Reissues, see below*

Large Entity Fee Code	($)	Small Entity Fee Code	($)	Fee Description
103	18	203	9	Claims in excess of 20
102	78	202	39	Independent claims in excess of 3
104	260	204	130	Multiple dependent claim, if not paid
109	78	209	39	**Reissue independent claims over original patent
110	18	210	9	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 18.00

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	($)	Small Entity Fee Code	($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	380	216	190	Extension for reply within second month	
117	870	217	435	Extension for reply within third month	
118	1,360	218	680	Extension for reply within fourth month	
128	1,850	228	925	Extension for reply within fifth month	
119	300	219	150	Notice of Appeal	
120	300	220	150	Filing a brief in support of an appeal	
121	260	221	130	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,210	241	605	Petition to revive - unintentional	
142	1,210	242	605	Utility issue fee (or reissue)	
143	430	243	215	Design issue fee	
144	580	244	290	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	760	246	380	Filing a submission after final rejection (37 CFR 1.129(a))	
149	760	249	380	For each additional invention to be examined (37 CFR 1.129(b))	
				Other fee (specify) _____	
				Other fee (specify) _____	

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($)

SUBMITTED BY				Complete (if applicable)	
Typed or Printed Name	Steven R. Crowley			Reg. Number	31,604
Signature		Date	11/10/2000	Deposit Account User ID	

Practitioner's Docket No. 6488.US.02 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Steven L. Krill *et al.*
Serial No.: Group No.:
Filed: November 8, 2000 Examiner:
For: SOLID DISPERSION PHARMACEUTICAL FORMULATIONS

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

EXPRESS MAIL CERTIFICATE

"Express Mail" label number EL 384 167 796 US
Date of Deposit: November 10, 2000

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Utility Patent Application Transmittal, 2 pages
Fee Transmittal (In duplicate)
Specification (21 pages); Claims (7 pages); Abstract (1 page); Drawings (5 pages); **Total: 34**
Declaration and Power of Attorney (Unexecuted), 3 pages
Information Disclosure Statement
Form PTO-1449, in duplicate
Eight (8) cited references as listed on Form PTO-1449
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Kathleen T. Litz

Kathleen T. Litz 11/10/2000
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SOLID DISPERSION PHARMACEUTICAL FORMULATIONS

This application claims the benefit of U.S. Provisional Application for Patent No. 06/165,018, filed November 12, 1999.

Technical Field of the Invention

The instant invention relates to the fields of pharmaceutical and organic chemistry, and provides novel solid dispersion pharmaceutical formulations with enhanced bioavailability.

Background of the Invention

One measure of the potential usefulness of an oral dosage form of a pharmaceutical agent is the bioavailability observed after oral administration of the dosage form. Various factors can affect the bioavailability of a drug when administered orally. These factors include aqueous solubility, drug absorption throughout the gastrointestinal tract, dosage strength, and first pass effect. Aqueous solubility is one of the most important of these factors. When a drug has poor aqueous solubility, attempts are often made to identify salts or

other derivatives of the drug which have improved aqueous solubility. When a salt or other derivative of the drug is identified which has good aqueous solubility, it is generally accepted that an aqueous solution formulation of this salt or derivative will provide the optimum oral bioavailability. The bioavailability of the aqueous oral solution formulation of a drug is then generally used as the standard or ideal bioavailability against which other oral dosage forms are measured.

For a variety of reasons, including patient compliance and taste masking, a solid dosage form, such as a capsule or tablet, is usually preferred over a liquid dosage form. However, oral solid dosage forms of a drug generally provide a lower bioavailability than oral solutions of the drug. One goal of the development of a suitable solid dosage form is to obtain a bioavailability of the drug that is as close as possible to the ideal bioavailability demonstrated by the oral aqueous solution formulation of the drug.

An alternative dosage form is a solid dispersion. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at

solid state prepared by the melting (or fusion), solvent, or melting-solvent methods. (Chiou and Riegelman, *Journal of Pharmaceutical Sciences*, *60*, 1281 (1971)). The dispersion of a drug or drugs in a solid diluent by mechanical mixing is not included in this category. Solid dispersions may also be called solid-state dispersions.

Retroviral protease inhibiting compounds are useful for inhibiting HIV proteases *in vitro* and *in vivo*, and are useful for inhibiting HIV (human immunodeficiency virus) infections and for treating AIDS (acquired immunodeficiency syndrome). HIV protease inhibiting compounds typically are characterized by having poor oral bioavailability. Examples of HIV protease inhibiting compounds include 2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);

(2S, 3S, 5S)-2-(2,6-Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methy l butanoyl]-amino-1,6-diphenylhexane (ABT-378);

N-(2(R)-hydroxy-1 (S)-indanyl)-2(R)-phenylmethyl

-4(S)-hydroxy-5-(l-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcar
boxamido)-piperazinyl))-pentaneamide (indinavir);
N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2
-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-iso
quinoline-3(S)-carboxamide (saquinavir);
5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-
phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;
1 -Naphthoxyacetyl-beta-methylthio-Ala-(2S, 3S)-
3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4-
t-butylamide;
5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-
amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-
butylamide;
[1S-[1R-(R-),2S*])-N^1 [3-[[[(1,1 -
dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-
hydroxy-1-(phenylmethyl)propyl]-2-[(2-
quinolinylcarbonyl)amino]-butanediamide;
VX-478; DMP-323; DMP-450; AG1343 (nelfinavir);
BMS 186,318; SC-55389a; BILA 1096 BS; and U-140690, or
combinations thereof.

While some drugs would be expected to have good solubility in organic solvents, it would not necessarily

follow that oral administration of such a solution would give good bioavailability for the drug.

Polyethylene glycol (PEG) solid dispersion formulations are generally known to improve the dissolution and bioavailability of many compounds. However, Aungst *et al.* has recently demonstrated that this was unable to improve the bioavailability of an HIV protease inhibitor with a cyclic urea structural backbone, called DMP 323 (Aungst *et al.*, *International Journal of Pharmaceutics, 156*, 79 (1997)).

Thus, it would be a significant contribution to the art to provide a solid dispersion pharmaceutical formulation of a retroviral protease inhibitor which is more stable and has enhanced bioavailability.

Summary of the Invention

The instant invention provides a stable solid dispersion comprising a retroviral protease inhibitor and PEG having improved bioavailability.

Also provided by the instant invention is a pharmaceutical composition comprising a stable solid dispersion as described above with a pharmaceutically acceptable carrier, diluent, or excipient.

Additionally provided by the instant invention is a method for preparing a stable solid dispersion as described above.

The instant invention still further provides a method of treating an HIV infection comprising administering an effective amount of a stable solid dispersion as described above to a mammal in need of such treatment.

Brief Description of the Figures

Figure 1 illustrates the dispersion of amorphous ABT-538 in PEG 8000.

Figure 2 illustrates the bioavailability of a dispersion of amorphous ABT-538 in PEG 8000.

Figure 3 illustrates the in vivo-in vitro correlation of ABT-538.

Figure 4 illustrates the dissolution of ABT-378.

Figure 5 illustrates the dissolution of nelfinavir.

Detailed Description of the Invention

This invention pertains to the preparation of solid dispersion systems for protease inhibitors with improved dissolution and oral bioavailability.

A solid (molecular) dispersion comprising an HIV protease inhibiting compound may be prepared by dissolving or dispersing the HIV protease inhibiting compound in a sufficient amount of an organic solvent followed by dispersion into a suitable water soluble carrier. Suitable organic solvents include pharmaceutically acceptable solvents such as methanol, ethanol, or other organic solvents in which the protease inhibitor is soluble. Suitable water soluble carriers include polymers such as polyethylene glycol (PEG), pluronics, pentaeythritol, pentaeythritol tetraacetate, polyoxyethylene stearates, poly-ε-caprolactone, and the like.

The organic solvent (preferably ethanol) may then be evaporated away, leaving the drug dispersed/dissolved in the molten matrix, which is then cooled. The solid matrix has the compound finely dispersed (molecular dispersion) in such a way that dissolution of the drug is maximized, thus

improving the bioavailability of a drug exhibiting dissolution rate limited absorption. Ease of manufacturing is also an attribute to this type of formulation. Once the organic solvent is evaporated to yield a solid mass, the mass may be ground, sized, and optionally formulated into an appropriate delivery system. Thus, by improving the dissolution of a poorly water soluble drug, the drug in a suitable carrier may be filled into a gelatin capsule as a solid, or the matrix may potentially be compressed into a tablet.

The delivery system of the present invention results in increased solubility and bioavailability, and improved dissolution rate of the HIV protease inhibiting compound.

Other pharmaceutically-acceptable excipients may be added to the formulation prior to forming the desired final product. Suitable excipients include lactose, starch, magnesium stearate, or other pharmaceutically-acceptable fillers, diluents, lubricants, disintegrants, and the like, that might be needed to prepare a capsule or tablet.

The resulting composition comprising the HIV protease inhibiting compound may be dosed directly for oral administration, diluted into an appropriate vehicle for

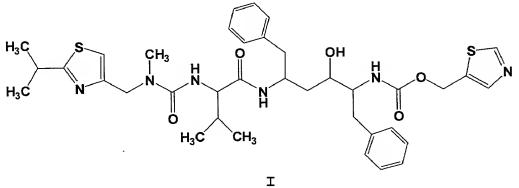
oral administration, filled into capsules, or made into tablets for oral administration, or delivered by some other means obvious to those skilled in the art. The composition can be used to improve the oral bioavailability and solubility of said HIV protease inhibiting compound.

Total daily dosing of HIV protease inhibitors may be administered to a human in single or divided doses in amounts, for example, from 0.001 to 1000 mg/kg body weight daily, but more usually 0.1 to 50 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, rate of excretion, drugs administered in combination and the severity of the particular disease undergoing therapy.

ABT-538 (ritonavir) was preferably used as the HIV protease inhibitor in the instant invention. Additionally, two other protease inhibitors, ABT-378 and nelfinavir mesylate, were tested in solid dispersions to demonstrate

the improved dissolution which can be achieved with this system.

One aspect of the instant invention provides a solid dispersion of a compound of formula I

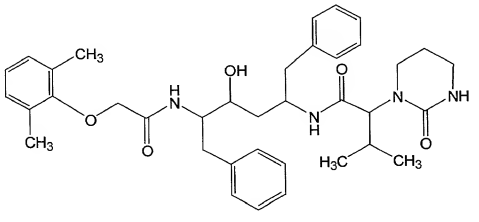


I

A compound of formula I is an HIV protease inhibitor marketed by Abbott Laboratories under the tradename Norvir®, with the common name ritonavir [(2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)-methyl)amino)carbonyl)-L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-1,6-diphenyl-3-hydroxyhexane]. This and other compounds as well as methods for preparing same are disclosed in U.S. Patent

Nos. 5,648,497 and 5,541,206, the disclosures of which are herein incorporated by reference.

Additional HIV protease inhibitors which may be formulated into a solid dispersion include compounds of formula II

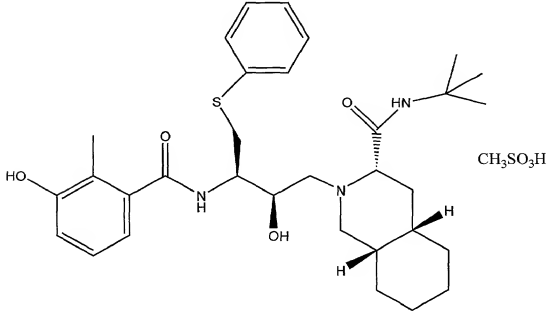


II

A compound of formula II is known as ABT-378 ((2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)-amino-3-hydroxy-5-(2S-(1-tetrahydropyrimid-2-onyl)-3-methyl-butanoyl)amino-1,6-diphenylhexane). This and other compounds, as well as methods for preparing same, are

identified in U.S. Patent No. 5,914,332, the disclosure of which is herein incorporated by reference.

A compound of formula III provided hereinbelow is known as nelfinavir mesylate (marketed under the tradename Viracept® by Agouron Pharmaceuticals, Inc. in La Jolla, CA), and is another HIV protease inhibitor which may be formulated into a solid dispersion.



III

The following Examples are provided to further illustrate the present invention.

EXAMPLES

Example 1

Dispersion Preparations

A. Ritonavir (ABT-538) Dispersion Preparation:

The samples were prepared by dissolving ABT-538 in a small volume of 200 proof ethanol in a 250 ml round bottom flask. The flask was vortexed and then placed in a water bath maintained at 75 °C. The PEG 8000 was added to the hot alcohol solution with continual swirling until the PEG melted. The flask was then attached to a rotary evaporator, immersed in the water bath (75 °C) under vacuum for 15 minutes to remove the ethanol. After the majority of ethanol had evaporated, the flask was immersed in an ice bath for 15 minutes. The contents of the flask were then vacuum dried at room temperature for 6 hours. The solid was transferred to a crystallization dish and placed under vacuum overnight to remove residual ethanol. The material was then ground and sifted. Particles ranging in size from

149 to 420 μm were used for further studies. The drug loads used for these dispersions were 10, 20 and 30% w/w.

B. ABT-378 Dispersion Preparation:

A 10% dispersion was prepared using an alcoholic solution of ABT-378 (ca. 0.1 g/ml) by the same method as described in section A above.

C. Nelfinavir mesylate Dispersion Preparation:

Nelfinavir mesylate is available from Agouron Pharmaceuticals, Inc. under the tradename Viracept®.

A 10% dispersion was prepared using an alcoholic solution of nelfinavir (ca. 0.035 g/ml) by the same method as described in section A above.

The potency values of all the dispersions as well as the dissolution sample concentrations were determined via HPLC.

D. Results:

The *in vitro* dissolution data of the ABT-538 dispersions compared with ABT-538 in 0.1*N* HCl (shown in Figure 1, n=3 ± SD unless otherwise indicated) show that the dispersions markedly improved the dissolution rate of the drug. Drug loading decreases the rate of drug release in a rank order. A bioavailability study was conducted in

dogs with the above ABT-538 dispersions to elicit the drug load effects *in vivo*. Eight beagle dogs, obtained from Marshall Research Animals (North Rose, NY), were utilized in this study. The animals were fasted overnight prior to dosing in each period but water was allowed *ad libitum*. Approximately 30 minutes prior to dosing, each dog received a 100 μg/kg subcutaneous dose of histamine. Capsules containing 5 mg/kg of 10, 20 and 30% solid dispersion (formulations A, B and C, respectively) were tested against crystalline drug as a reference in a four-way crossover study.

Each dog received the dose followed by approximately 10 ml of water. A washout period of approximately 1 week was used to separate each dosing period. The plasma samples were analyzed by a method reported by Marsh *et al.* (Marsh, K.C., Eiden, E. and McDonald, E. Determination of Ritonavir, a new HIV Protease Inhibitor, in Biological Samples Using Reversed-Phase High-Performance Liquid Chromatography. *J. Chromatography B.* 704 (1997) 307-313.)

The results of the study are shown in Figure 2. The results show that the solid dispersions improve absorption compared to the reference. An *in vitro - in vivo*

correlation was established. A plot of the AUC versus the amount dissolved in 20 min, shown in Figure 3, is a straight line, indicating excellent correlation.

The dissolution properties of the two additional protease inhibitors (ABT-378 and nelfinavir mesylate) were also determined. The *in vitro* dissolution data (Figure 4) of the ABT-378 dispersion compared with reference clearly shows that the preparation of a dispersion markedly improves dissolution rate of the drug. The variability in the release rate from the dispersion is due to the fact that the preparation of these dispersions had not been optimized to completely overcome the wetting problem of the drug. Despite this, the improvements observed are significant [95% confidence intervals shown].

The nelfinavir mesylate solid dispersion also exhibits an improved *in vitro* dissolution rate compared to the neat drug (Figure 5).

E. Conclusions:

Solid dispersions of HIV protease inhibitors (for example, ABT-538 (ritonavir), ABT-378, and nelfinavir mesylate) markedly improve the dissolution rate of these

drugs. This improvement of dissolution rate is reflected in the improvement of bioavailability. An excellent *in vivo - in vitro* correlation established for the dispersions suggests that the *in vitro* dissolution reflects *in vivo* bioavailability for these systems.

Example 2

Stability of Dispersion in Molten PEG 8000

The stability of the dispersion of ABT-538 in PEG 8000 in the molten state at 70 °C was examined. Individual approximately 5 mg quantities of the dispersion (aged for 6 weeks at room temperature) were placed in 4 ml glass vials. These vials, with the exception of the initial time point, were placed in a
70 °C oven which was sampled at pre-determined intervals, chilled in ice water and placed in the freezer until HPLC analysis. After all samples were collected, they were analyzed for ABT-538 content by HPLC. The HPLC system consisted of a Hitachi AS 4000 autosampler, SP 8800 ternary pump, Applied Biosystems 783 detector, and PE Nelson Data

acquisition system. Other chromatographic details included a Regis Little Champ 5 cm C-18 column, a mobile phase consisting of an aqueous solution of 0.1% trifluoroacetic acid in 10 mM aqueous tetramethyl ammonium perchlorate (TMAP)/acetonitrile/methanol (55/40/5). The flow rate was 1 ml/minute, the wavelength of detection was 205 nm, and the injection volume was 100 µl. Standard curves of peak area of ABT-538 vs. concentration in the range of interest were compared with experimentally obtained area counts.

Example 3

Additional Protocol For Oral Bioavailability Studies

Dogs (beagle dogs, mixed sexes, weighing 7-14 kg) are fasted overnight prior to dosing, but are permitted water *ad libitum*. Each dog receives a 100 µg/kg subcutaneous dose of histamine approximately 30 minutes prior to dosing. Each dog receives a single solid dosage form corresponding to a 5 mg/kg dose of the drug. The dose is followed by approximately 10 milliliters of water. Blood samples are obtained from each animal prior to dosing and at 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after drug

administration. The plasma is separated from the red cells by centrifugation and frozen (- 30 °C) until analysis. The concentrations of parent drug is determined by reverse phase HPLC with low wavelength UV detection following liquid-liquid extraction of the plasma samples. The parent drug area under the curve is calculated by the trapezoidal method over the time course of the study. The absolute bioavailability of each test composition is calculated by comparing the area under the curve after oral dosing to that obtained from a single intravenous dose. Each capsule or capsule composition is evaluated in a group containing at least six dogs. The values reported are averages for each group of dogs.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising a solid dispersion of an HIV protease inhibitor or combination of HIV protease inhibitors and a water soluble carrier.

2. The composition of Claim 1 wherein said water soluble carrier is polyethylene glycol (PEG).

3. The composition of Claim 1 wherein said HIV protease inhibitor is dissolved in an organic solvent.

4. The composition of Claim 3 wherein said organic solvent is ethanol.

5. The composition of Claim 2 wherein said HIV protease inhibitor is selected from the group consisting of:

2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-

thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir);

(2S, 3S, 5S)-2-(2,6Dimethylphenoxyacetyl) amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378);

N-(2(R)-hydroxy-1 (S)-indanyl)-2(R)-phenylmethyl -4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide (indinavir);

N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (saquinavir);

5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide;

1 -Naphthoxyacetyl-beta-methylthio-Ala-(2S, 3S)-3-amino-2-hydroxy-4-butanoyl 1,3-thiazolidine-4-t-butylamide;

5-isoquinolinoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide;

[1S-[1R-(R-),2S*])-N^1-[3-[[[(1,1 -dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1 -(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;

VX-478; DMP-323; DMP-450; AG1343 (nelfinavir); BMS 186,318; SC-55389a; BILA 1096 BS; U-140690, or combinations thereof.

6. The composition of Claim 2 wherein said HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

7. The composition of Claim 2 wherein said HIV protease inhibitor is (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl-butanoyl] amino-1,6-diphenylhexane (ABT-378).

8. The composition of Claim 2 wherein said HIV protease inhibitor is a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-

hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

9. The composition of Claim 2 wherein said solid dispersion is encapsulated in a hard gelatin capsule.

10. The composition of Claim 2 wherein said solid dispersion is compressed into a tablet.

11. The composition of Claim 1 further comprising an additive or a mixture of additives independently selected from the group consisting of pharmaceutically acceptable surfactants and antioxidants.

12. A method of preparing a composition of Claim 1 which comprises:

a) dissolving an HIV protease inhibitor into an organic solvent to form a solution;

b) adding a water soluble carrier to said solution to form a mixture;

c) optionally flash evaporating said solvent;

d) optionally drying the resulting residue remaining after evaporation;

e) optionally grinding and sieving the solid dispersion to obtain a resultant product.

13. The method of Claim 12 additionally comprising encapsulating the solid dispersion in a hard gelatin capsule.

14. The method of Claim 12 additionally comprising compressing said solid dispersion into a tablet.

15. The method of Claim 12 wherein said HIV protease inhibitor is (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir).

16. The method of Claim 12 wherein said HIV protease inhibitor is (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-

pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

17. The method of Claim 12 wherein said solvent is ethanol.

18. The method of Claim 12 wherein said water soluble carrier is polyethylene glycol (PEG).

19. A method of treating an HIV infection comprising administering an effective amount of a solid dispersion of Claim 1 to a mammal in need of such treatment.

20. The method of Claim 19 wherein said HIV protease inhibitor is selected from the group consisting of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

21. The method of Claim 19 wherein said HIV protease inhibitor is a combination of (2S,3S,5S)-5-(N-(N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)L-valinyl)amino-2-(N-((5-thiazolyl)methoxy-carbonyl)-amino)-amino-1,6-diphenyl-3-hydroxyhexane (ritonavir) and (2S,3S,5S)-2-(2,6-Dimethylphenoxyacetyl)amino-3-hydroxy-5-[2S-(1-tetrahydro-pyrimid-2-onyl)-3-methyl butanoyl] amino-1,6-diphenylhexane (ABT-378).

Abstract

A pharmaceutical composition is disclosed which comprises a solid dispersion of an HIV protease inhibitor in a water soluble carrier, such as PEG, having enhanced bioavailability and improved dissolution properties. The solid dispersion may optionally be encapsulated in hard gelatin capsules, compressed into a tablet, or may be granulated with a pharmaceutically acceptable granulating agent. Also disclosed are methods of making said solid dispersion and methods of treating an HIV infection employing said solid dispersion.

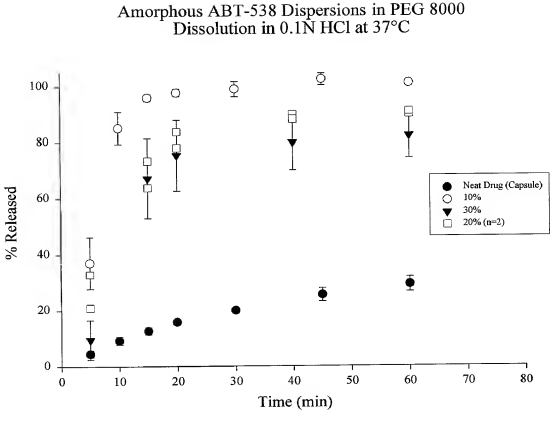

Amorphous ABT-538 Dispersions in PEG 8000
Dissolution in 0.1N HCl at 37°C
% Released
Time (min)
0
20
40
60
80
100
0
10
20
30
40
50
60
70
80
Neat Drug (Capsule)
10%
30%
20% (n=2)

Figure 1

Amorphous ABT-538 Dispersions in PEG 8000
(Crossover Design, n=7)

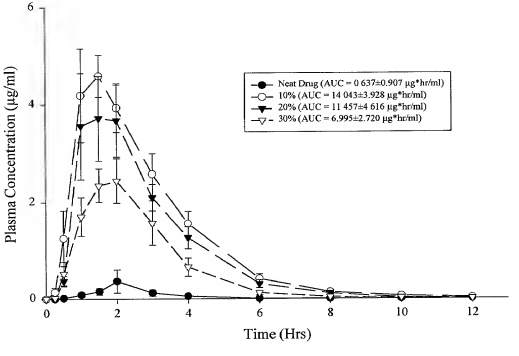


Figure 2

IVIV Correlation
Dog Studies 5 mg/Kg and Dissolution in 0.1N HCl at 37°C, 50 rpm

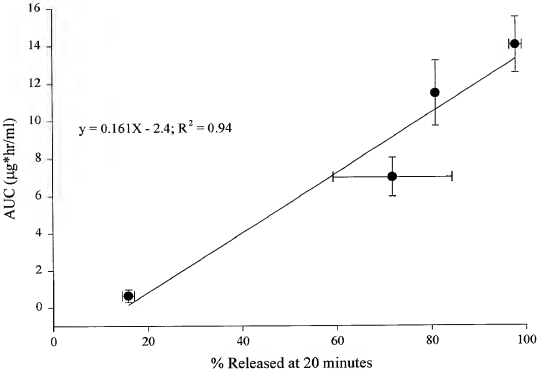


Figure 3

ABT-378 Dissolution in 0.1 N HCl at 37°C
(3.6 mg drug per capsule)

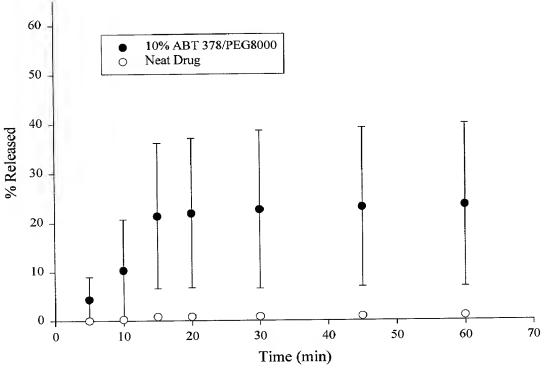


Figure 4

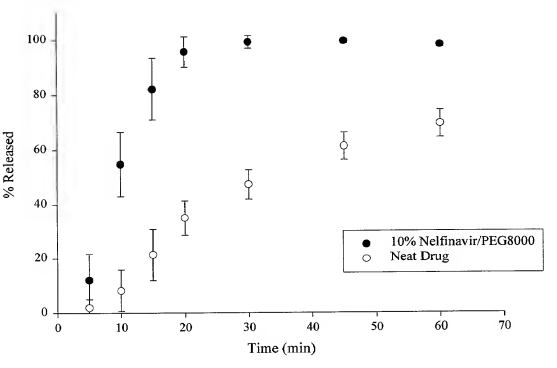

Nelfinavir Dissolution in 0.1N HCl at 37°C
(25 mg per capsule)
% Released
Time (min)
10% Nelfinavir/PEG8000
Neat Drug
0
20
40
60
80
100
0
10
20
30
40
50
60
70

Figure 5

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): S. L. Krill *et al.*

Serial No.:

Filed: November 8, 2000

For: SOLID DISPERSION PHARMACEUTICAL FORMULATION

Case No.: 6488.US.02

Examiner: Not Yet Assigned

Date: November 10, 2000

Certificate of Mailing Under 37 C.F.R. §1.8(a)
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I hereby certify that this paper (along with any Paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below as Express Mail Post Office to Addressee Service under 37 CFR 1.10 addressed to:

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Date of Deposit: November 10, 2000

Signature: Kathleen T. Litz 11/10/2000
Kathleen T. Litz Date

Declaration and Power of Attorney for a United States Patent Application

As a below-named inventor, I hereby declare:

My residence, post office address and citizenship are as stated below next to my name. I believe I am an original and first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled **SOLID DISPERSION PHARMACEUTICAL FORMULATION** the specification of which is enclosed herewith

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims.

I acknowledge a duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

Claim to benefit of foreign application(s) as follows:

I hereby claim foreign priority benefits under 35 U.S.C. §119 for the following foreign application(s) for patent or inventor's certificate:

NONE

The following foreign applications for patent or inventor's certificate have a filing date earlier than the filing date of the application(s) identified above:

NONE

Claim to benefit of earlier U.S. application(s) as follows:

I hereby claim the benefit under 35 U.S.C. §120 of the following earlier-filed United States patent application(s). Insofar as the subject matter of each of the claims of this/these application(s) is not disclosed in the prior U.S. applications in the manner required by 35 U.S.C. §112, first paragraph, I acknowledge a duty to disclose to the Patent and Trademark Office all information known to me to be material to patentability as defined in 37 C.F.R. §1.56 which came into existence between the filing date(s) of the prior applications and the national or PCT filing date of this application.

I hereby claim the benefit under Title 35, United States Code § 119 (e) of any United States provisional application(s) listed below.

Serial No.: 60/165,018 Filed: November 12, 1999

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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that all statements made herein were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

James J. Fort	Date	Steven L. Krill	Date
Devalina Law	Date	Yihong Qiu	Date
William R. Porter	Date	Erica A. Schmitt	Date